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Deaeration Techniques For Dissolution Media

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Summary

Sixteen deaeration methods were evaluated for effectiveness using a dissolved oxygen sensor. Assuming that any method which deaerates water to less than or equal to 95% of saturation at 37°C is adequate, techniques shown to be acceptable include vacuum filtration, helium sparging, hot water placed under a vacuum with or without sonication, and use of a Media Mate. Media shown to be unacceptable with respect to deaeration include room temperature tap water with no treatment, placed under vacuum, or placed under vacuum with sonication. Hot tap water with no treatment or with sonication produces mean values below 100% saturation, but greater than the recommended 95% saturation value. We also demonstrate that no special precautions are needed when transferring deaerated media to dissolution vessels. In addition, we show that stirring to accelerate thermal equilibration is acceptable since oxygen concentrations remain well below saturation during that time period.

Introduction

The purpose of a dissolution apparatus is to provide a consistent and reproducible hydrodynamic profile at the formulation-media interface. Any factor that changes the hydrodynamic profile risks disrupting the consistency and reproducibility of a dissolution test. Air bubbles have been speculated to affect dissolution results in a number of ways. [1,2] Bubbles forming on the apparatus may change the fluid flow characteristics and thereby change the effective shear at the formulation-media boundary. Bubbles forming on the dosage form can provide a barrier to wetting and dissolution, or can change dispersion characteristics of particles and aggregates. The degree to which air in media can affect dissolution results has been recently studied by compiling instances of apparatus calibration failures. [3] For tests using non-deaerated media, failure rates were significantly higher than when most forms of deaerated media were used.

The relevance of the effect of deaeration on dissolution of a particular formulation or product can only be judged on a case-by-case basis. To maintain consistency between runs and to avoid yet another variable when trying to transfer assays between labs, we typically specify deaerated media in assay procedures. There has, however, been some debate over the most appropriate method to deaerate dissolution media, but most reports are anecdotal. To provide quantitative data to add substance to the debate, we undertook a study to compare various deaeration methods.

Experimental

Henry's Law states that at low concentration, the mole fraction of a solute is proportional to its vapor pressure. We assume that water containing dissolved gases behaves as an ideal dilute solution so that the relative saturation of oxygen in water is an effective measure of the relative air saturation.

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Oxygen Measurements To measure dissolved oxygen, an Orion Model 97-08-99 O_2 Electrode and Orion Model 420A pH Meter, or Corning M90 Dissolved Oxygen Meter were used. Deionized tap water was subjected to various treatments and used as test media. The most relevant point in time to measure deaeration effectiveness is just before introduction of the dosage form. Oxygen values were therefore collected after media had been dispensed into the dissolution apparatus vessels and allowed to equilibrate with no stirring to 37°C.

Deaeration Conditions Sixteen deaeration conditions were tested. To provide a constant benchmark, air saturated 37°C water was prepared by bubbling air via an HPLC TEFLON solvent inlet filter through a vessel of water placed in a thermostatted water bath. Except for water dispensed by a Hanson Media Mate, all media were prepared in a 4 liter thick-walled glass vessel, then poured into the 1 liter flasks in a dissolution rate apparatus. No stirring or swirling of media was employed during deaeration. Combinations of the following conditions were tested.

Initial Water Temperature Both room temperature and hot deionized tap water was available in house. Room temperature deionized water varied in temperature between about 21° and 25 °C. Hot deionized tap water temperature varied between about 45° and 50 °C.

Vacuum House vacuum pressure was measured by manometer to fluctuate between 7 to 10 mm H. When used, vacuum was applied for 5 minutes.

Sonication Sonication was performed with a Branson 5210 ultrasonic bath with 185 W input power and 47 kHz frequency. When used, sonication was applied for 5 minutes.

Filtration Water was vacuum filtered through either a 350 ml Kimax Buchner funnel with coarse fritted disk (40-60 µm pore size), a 350 ml Kimax Buchner funnel with medium fritted disk (10-15 µm pore size), or through a 300 ml glass funnel/support assembly fitted with a 0.45 µm membrane filter. Disk/frit diameter was 47 mm.

Helium Sparging Helium was bubbled through water via an HPLC Teflon solvent inlet filter. Helium flow rate was about 900 ml/min. When used, sparging occurred for 5 minutes.

Results and Discussion

When deciding which deaeration method to use, rather than debating which method is best, a more appropriate question to ask is whether the method used is adequate. Hanson states that to avoid deaeration problems, media should be at least 5% below saturation at the operating temperature. [1] We will for this study assume that any method that deaerates to below a target value of about 95% of saturation is acceptable.

Figure 1 contains the mean percent oxygen saturation obtained by the various methods. The error bar represents the standard deviation of measurements on three separate flasks. It is readily apparent that there are several methods which do not deaerate adequately. Room temperature tap water with no treatment, placed under vacuum, or even placed under vacuum with sonication is not sufficiently degassed. Hot tap water with no treatment or with sonication produces mean values

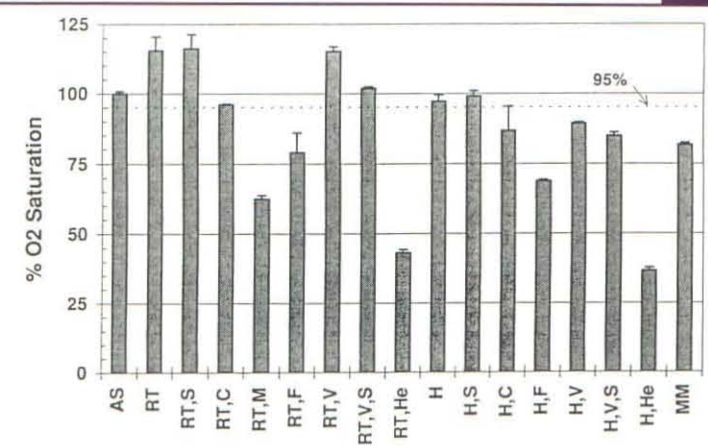

Figure 1. Percent oxygen saturation for deaeration methods. See text for descriptions of methods. Abbreviations: AS = Air Saturated; RT = Room Temperature Initially; H = Hot Initially; S = Sonicated; V = Vacuum; C = Coarse Frit Filter; M = Medium Frit Filter; F = 0.45 pm Membrane Filter; He = Helium Sparged; MM = Media Mate. The recommended 95% saturation level for deaeration is also displayed.

below saturation, but greater than Hanson's recommended 95% saturation value. Sonication appears to enhance degassing efficiency when combined with vacuum, but has no measurable effect when performed alone.

Adequate deaeration techniques include vacuum filtration, helium sparging, hot water placed under a vacuum with or without sonication, and use of a Media Mate. The manual method suggested by the USP includes both heating the water to 45°C then vacuum filtering it through a 0.45 micron pore size filter. Our data suggests

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vacuum filtration alone provides sufficient deaeration and that heating is an unnecessary extra step.

In addition to acceptability of the deaeration level, one must also consider the factors of time and convenience, i.e., how quick and easy is the deaeration method? Vacuum filtration with either the medium frit or the 0.45 pm pore disk took a significant amount of time, about 2-5 min per liter, and it was necessary to constantly refill the funnel. With a larger funnel and frit/disk size, filtration time and number of funnel refills could be reduced. Filtering with the coarse frit was very quick, almost as fast as media was poured into the Buchner funnel. Helium sparging is the most effective means tested to deaerate media and is relatively efficient since media can be made in large batches. A disadvantage, though, is that helium is expensive. Vacuum and vacuum with sonication methods are relatively fast if one has ready access to hot deionized water. The Media Mate can rapidly dispense 37°C thermally equilibrated deaerated water, but its size and calibration issues may make it inconvenient for some labs.

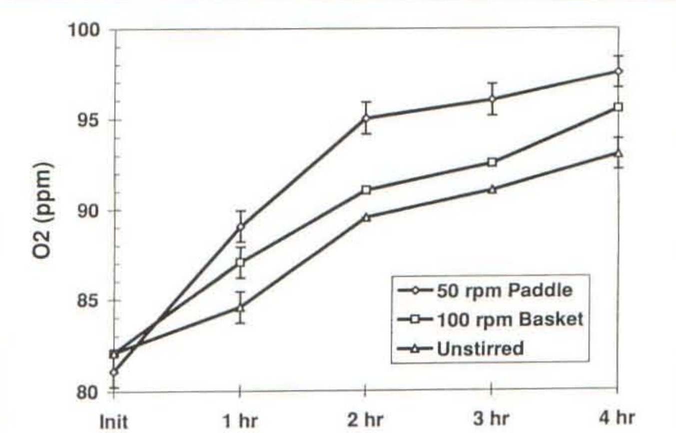

Figure 2. Oxygen equilibration profiles for 37°C deaerated water in vessels stirred with 50 rpm paddles, 100 rpm baskets, and vessels left unstirred.

Other Considerations

Two other practical considerations when performing dissolution testing with deaerated water concern transfer of media and equilibration to testing temperature. It has been stated that media should be poured gently into the dissolution vessels. [2,4] We tested this requirement by pouring hot, 0.45 micron filtered water both down the sides of the vessels (our interpretation of gently) and directly into the center of the vessels. Oxygen levels from both practices were not statistically different: 4.38 + 0.04 and 4.35 + 0.08 ppm for gentle and "turbulent" transfer respectively. We conclude that if good laboratory practice is followed, i.e., there is no loss of media from spilling or splashing, no extra-special care need be taken when transferring media.

Media are often.stirred in order to reduce thermal equilibration times. A simple evaluation in our lab revealed 52.7°C equilibrated to 37.5°C by 30 minutes in stirred vessels compared to 43 min. in unstirred vessels. It has been suggested, however, that one should not stir dissolution media during thermal equilibration since air could be re-introduced. [2] From a practical perspective, if air saturation occurs much more slowly than temperature equilibration, stirring the media to reduce the equilibration time is acceptable.

We tested the kinetics of oxygen equilibration of deaerated water. Thermally equilibrated 37°C water was dispensed from a Media Mate into dissolution vessels. Oxygen concentrations were measured initially and at subsequent time points in vessels stirred with 50 rpm paddles or 100 rpm baskets, and vessels left unstirred. Measured oxygen concentrations to four hours are shown in Figure 2. While oxygen re-equilibration is faster in stirred than unstirred media, oxygen concentrations are well below saturation for all three conditions in the time required for thermal equilibration. Stirring media during temperature equilibration is therefore an acceptable practice.

Final Thoughts

Presented here are data to support several deaeration techniques. Applicability and convenience of a particular method should be assessed by individual labs. If a deaeration technique not covered here is in question, a simple measurement with a dissolved oxygen sensor will provide the data necessary to validate the method.

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